Omega-3 DHA and EPA for Cognition, Behavior, and Mood: Clinical Findings and Structural-Functional Synergies with Cell Membrane Phospholipids

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Abstract

The omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are orthomolecular, conditionally essential nutrients that enhance quality of life and lower the risk of premature death. They function exclusively via cell membranes, in which they are anchored by phospholipid molecules. DHA is proven essential to pre- and postnatal brain development, whereas EPA seems more influential on behavior and mood. Both DHA and EPA generate neuroprotective metabolites. In double-blind, randomized, controlled trials, DHA and EPA combinations have been shown to benefit attention deficit/hyperactivity disorder (AD/HD), autism, dyspraxia, dyslexia, and aggression. For the affective disorders, meta-analyses confirm benefits in major depressive disorder (MDD) and bipolar disorder, with promising results in schizophrenia and initial benefit for borderline personality disorder. Accelerated cognitive decline and mild cognitive impairment (MCI) correlate with lowered tissue levels of DHA/EPA, and supplementation has improved cognitive function. Huntington disease has responded to EPA. Omega-3 phospholipid supplements that combine DHA/EPA and phospholipids into the same molecule have shown marked promise in early clinical trials. Phosphatidylserine with DHA/EPA attached (Omega-3 PS) has been shown to alleviate AD/HD symptoms. Krill omega-3 phospholipids, containing mostly phosphatidylcholine (PC) with DHA/EPA attached, markedly outperformed conventional fish oil DHA/EPA triglycerides in double-blind trials for premenstrual syndrome/dysmenorrhea and for normalizing blood lipid profiles. Krill omega-3 phospholipids demonstrated anti-inflammatory activity, lowering C-reactive protein (CRP) levels in a double-blind trial. Utilizing DHA and EPA together with phospholipids and membrane antioxidants to achieve a "triple cell membrane synergy" may further diversify their currently wide range of clinical applications. *(Altern Med Rev* 2007;12(3):207-227)

Introduction

The long-chain omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are conditionally essential nutrients now established to enhance life quality and lower the risk of premature death. They are orthomolecules whose functional sites are exclusively cell membranes, wherein they are structurally and functionally integrated via phospholipid molecules. Their confirmation as efficacious cardiovascular protectants has spurred research into their benefits for the human brain. This review focuses on their clinical roles in cognition, behavior, and mood and on their potentially synergistic interactions with the cell membrane phospholipid nutrients.

Adequate dietary availability of DHA and EPA is fundamental to brain function. DHA/EPA are important throughout adulthood, as well as during the brain growth spurts that characterize prenatal and postnatal development. Dietary supplementation with DHA and EPA has proven beneficial for many of the known higher mental functions.

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Among the proven brain benefits of DHA/EPA are the perinatal development of visual and other sensory functions; perinatal emergence of cognitive function and maintenance throughout life; behavior management; and mood control (e.g., the mood swings of bipolar disorder or symptoms of major depressive disorder (MDD)). The substantial clinical evidence that supports these applications is discussed in the sections that follow.

Omega-3s in Childhood Brain Development

During the last trimester of fetal life and the first two years of childhood, the brain undergoes a period of rapid growth – the "brain growth spurt."[1] Nutrient insufficiency during this period can compromise brain function. DHA is one nutrient absolutely required for the development of the sensory, perceptual, cognitive, and motor neural systems during the brain growth spurt.[1,2] EPA's importance for the brain's development *in utero* is unclear, but colostrum and breast milk contain EPA, albeit in lesser amounts than DHA.[3,4]

The fundamental importance of DHA for brain development is beyond dispute.[1] The neurons are continually forming axons and dendritic extensions with accompanying cell membranes. Growing membrane must be relatively fluid, and DHA is the most fluidizing element in cell membranes (discussed later in this review). Even the synapses that are the primary functional units of brain circuits are made from membranes preferentially enriched in DHA.[5]

The retina, functionally an extension of the brain, contains rods and cones with the most fluid membranes of all the body's cell types; they are also highly enriched in DHA. Laboratory animals (rodents, primates) with experimentally induced omega-3 deficiencies show deficits in retinal structure, visual acuity development, and cognitive performance.[6-8]

Perinatal Importance of DHA and EPA

Demand for DHA rises exponentially as the brain rapidly expands in the third trimester, and continues after birth as the baby interfaces with environmental stimuli. Infants born prematurely are at special risk for omega-3 insufficiency because they may not have benefited from a full trimester of the mother's lipid stores. Preterm infants have very limited ability to synthesize DHA from the shorter chain alpha-linolenic acid (ALA; C18:3).[2]

After birth, omega-3 status depends on the infant's innate lipid metabolism and dietary intake of breast milk or formula. Although DHA and EPA are prominent ingredients of breast milk, many infant formulas do not contain these nutrients. Supplementing the mother's diet with ALA is not a reliable means for obtaining DHA. In one study, lactating mothers received 10.7 g/day of ALA from flaxseed oil for four weeks. Breast milk levels of ALA, EPA, and DPA (docosapentaenoic acid; C22:5 omega-3) increased, but not that of DHA.[9]

All infants, whether preterm or full term, seem to require dietary DHA for retinal development and normal visual function. A meta-analysis evaluated studies on visual resolution acuity differences in healthy preterm infants, either supplemented or not supplemented with DHA.[2] Four prospective trials were included, providing data from both behavioral acuity tests and visual evoked potentials. Intake of DHA was correlated with significantly better visual resolution acuity at ages two months and four months. In another meta-analysis, this same research group found an advantage of DHA intake in full-term infants up to four months post-birth.[10]

McCann and Ames published an extensive review of the evidence that DHA is important for the development of cognition and other normal brain functions.[1] Their 258 references included meta-analyses, randomized controlled trials (RCT) on cognitive and behavioral performance, studies with rodents and non-human primates, and breastfeeding studies. Within the limits imposed by performance testing of infants and toddlers, they concluded that:

- In animals whose brain concentrations of DHA were severely reduced, dietary supplementation with DHA restored control performance levels.

- Studies with human infants suggest supplementation with DHA in formula or by boosting maternal levels enhances neuromotor development.

- Application of a wide range of tests yielded a positive association between breastfeeding and infant mental performance.

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Although it is difficult to test cognitive performance within the first year, infants who were fed breast milk or formulas with DHA were found (within a few months after birth) to have superior visual acuity compared to those fed less than adequate DHA. This superior visual function persists through the first year after birth[11] and perhaps into the seventh year or later.[12]

Treating Developmental Coordination Disorder/Dyspraxia

The importance of DHA/EPA for overall brain and motor development after birth is illustrated by dyspraxia, also known as developmental coordination disorder (DCD). DCD/dyspraxia involves specific impairments of motor function and seriously affects about five percent of school-aged children.[13] DCD's core motor deficits are often accompanied by difficulties with learning, behavior, and psychosocial adjustment that overlap with dyslexia and attention deficit/hyperactivity disorder (AD/HD) and often persist into adulthood.

A double-blind RCT was conducted on 117 children ages 5-12, using a mixed omega-3/omega-6 supplement versus an olive oil placebo.[13] The supplement was 80-percent fish oil and 20-percent evening primrose oil, with a 4:1 omega-3 to omega-6 ratio. The total daily dose provided 174 mg DHA, 558 mg EPA, and 60 mg omega-6 gamma-linolenic acid (GLA), plus 9.6 mg d-alpha tocopherol. Although the trial found no significant improvement in motor skills after three months, the researchers did report significant improvements in other areas.[13] The children who received the omega-3/omega-6 supplement showed three times the normal expected gain in reading skills and twice the normal gain in spelling competency, plus marked improvement in behavior. The children who received the olive oil placebo were switched to the omega-3/omega-6 supplement after three months and after three more months showed similar "catch-up" gains.

Other developmental brain disorders in children such as AD/HD and dyslexia overlap with DCD/dyspraxia and are also linked to apparent DHA/EPA deficits. Many of these children respond to oral supplementation of these nutrients, often administered with other nutrients as part of a comprehensive management regimen.[14,15]

Managing Attention Deficit/Hyperactivity Disorder

AD/HD is the most common childhood developmental disorder, with prevalence estimates ranging from 4-15 percent for school-age children in the United States and elsewhere (see Richardson, 2006 for a recent review[14]). Often AD/HD persists into adulthood. Considerable damage to the individual, family, and society can be exacerbated by co-morbidity with many other disorders of behavior, learning, or mood.[14,16] AD/HD children consistently exhibit abnormal fatty acid status.[14]

Several studies have reported reduced blood concentrations of highly unsaturated fatty acids (FAs) in AD/HD children compared to controls (reviewed by Richardson[14]). Typically, reductions have been found in DHA and total omega-3 FAs and in the omega-6 arachidonic acid (AA),[14] some of which may persist into adulthood.[17] In one study that included both AD/HD and non-AD/HD boys, low omega-3 levels were associated with a range of behavioral and learning problems, irrespective of the clinical diagnosis.[18] Whereas low blood omega-6 levels tend to correlate with some physical deficiencies, but not with cognitive or behavioral impairments, omega-3 deficiencies correlate with behavioral problems (conduct disorder, hyperactivity-impulsivity, anxiety, temper tantrums, sleep difficulties) and learning difficulties in children. Thus Richardson, in her insightful review, emphasized, "…omega-3 status is likely to be more relevant to AD/HD and related behavioral disorders."[14]

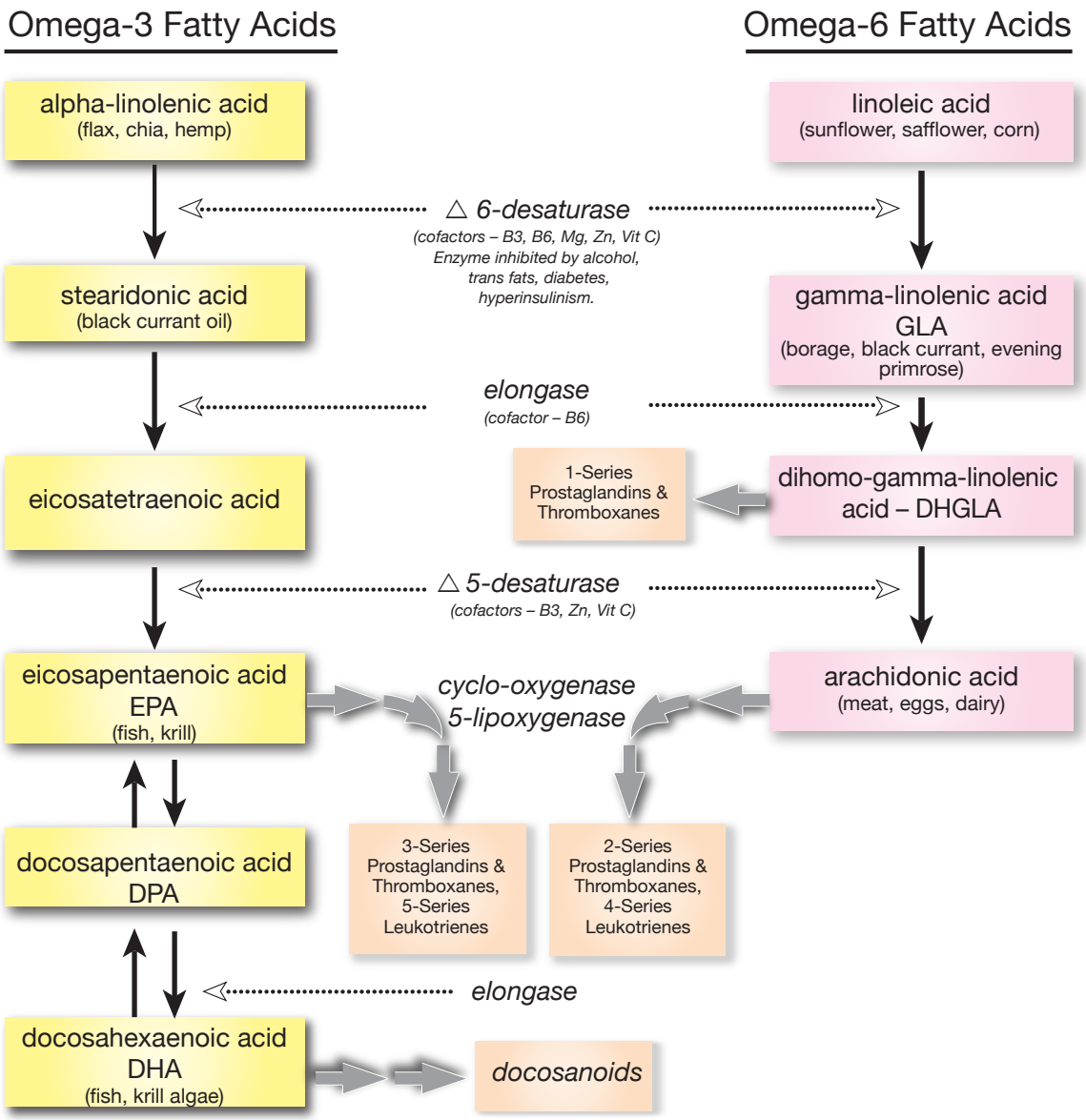
Clinical evidence from controlled trials, open studies, and case reports has yielded mixed results from DHA/EPA supplementation in AD/HD and its co-morbid conditions. In 2001, a double-blind RCT of omega-3 FAs was conducted on AD/HD children.[19] The 63 children ages 6-12 years were said to be receiving effective and stable treatment with stimulant medication, so this was an "add-on" study. They received daily adjunctive treatment of 345 mg pure DHA (from algae) or placebo. At the end of the four-month study, no changes were found on behavioral ratings or measures of inattention and impulsivity.

Similar negative findings came from a two-month, double-blind RCT of 40 AD/HD-type children ages 6-12 years in Japan.[20] Children were randomized

to receive either omega-3 fortified foods (providing approximately 510 mg DHA and 100 mg EPA per day) or indistinguishable control foods containing olive oil. Although no differences emerged on various cognitive tests, combined teacher and parent ratings found a greater reduction of aggression in the DHA group.[21]

A third double-blind RCT was conducted at Indiana's Purdue University on children with primarily AD/HD-type difficulties.[22] Fifty children (average age 10 years) were randomized to receive either an omega-3/omega-6 formula from fish oil plus evening primrose oil (each daily dose supplying 480 mg DHA, 80 mg EPA, 96 mg GLA, and 40 mg AA, plus 24 mg

Figure 1. Biosynthesis of the Principal Polyunsaturated Fatty Acids and Their Metabolites



alpha-tocopheryl acetate) or an olive oil placebo for four months. Significant benefits were found for attention and behavior and on clinical ratings of oppositional defiant disorder.

In 2002, Richardson and Puri published a double-blind RCT of 29 United Kingdom children with a primary diagnosis of dyslexia and secondary AD/HD-type symptoms.[23] Half the children received an omega-3/omega-6 combination with 480 mg DHA and 96 mg GLA as in the Purdue formula above, but with EPA higher at 186 mg, AA slightly higher at 42 mg, the omega-6 cis-linoleic acid at 864 mg, 60 IU vitamin E as dl-alpha tocopherol, and 8 mg thyme oil. The other half of the children received an olive oil "placebo" for three months. The omega-3/omega-6 combination produced significantly greater benefits than the olive oil for inattention, anxiety/withdrawal, and disruptive behavior. The authors noted the olive oil placebo could have contributed some benefit and that use of a truly inert placebo might have yielded a better overall trial outcome.

The shorter-chain ALA may not be as effective for AD/HD as DHA/EPA plus GLA. Thirty adults with AD/HD were randomized to supplementation with a large dose of 60 g/day of flaxseed oil, olive oil, or fish oil.[24] Serum phospholipid fatty acid status was determined at baseline and 12 weeks. Although flaxseed oil supplementation increased ALA levels of blood phospholipids, levels of EPA, DHA, and other omega-3 fatty acids were not increased; fish oil predictably increased EPA, DHA, and total omega-3s.

Thus, it appears a mix of DHA, EPA, and omega-6 fatty acids (GLA and AA) can improve the attention, learning, and behavioral afflictions typical of AD/HD, as well as co-morbidities such as anxiety/withdrawal, dyslexia, and aggression. There are numerous reports of low plasma and/or RBC omega-3 levels in AD/HD children and adults.[14] Recently, a specific gene polymorphism was discovered that is linked to clinical AD/HD and features suboptimal functioning of fatty acid desaturase enzymes.[25] Figure 1 illustrates the biosynthesis of the primary omega-3 and -6 fatty acids.

Ameliorating Aggression

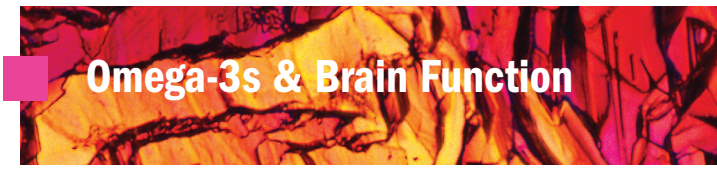
Hamazaki et al performed two double-blind trials with students clinically diagnosed as aggressive. In the 1996 trial,[26] 41 university students ages 21-30 were randomized to receive a DHA-rich fish oil providing 1.48-1.77 g/day DHA, 0.20-0.24 g/day EPA, and 0.10-0.12 g/day AA or control capsules of soy oil. The three-month trial was timed to end in the middle of the mental stress of challenging final exams. The DHA group demonstrated no increase in aggression during this stressful time; whereas, the control group demonstrated significant increases in aggression against others (extra-aggression). The researchers concluded DHA helped prevent extra-aggression from increasing at times of mental stress.

In 2005, the same research team conducted a three-month, double-blind trial on aggression involving 166 children ages 9-12 years.[27] The children received either omega-3 fortified foods that provided 3.6 g DHA and 0.84 g EPA *per week* or control foods with half soybean and half rapeseed oil. Physical aggression as assessed by a hostility-aggression questionnaire increased among girls in the control group but not among the girls who received omega-3s. Impulsivity was also significantly reduced among the omega-3 girls; no such differences were observed among the boys.

Clinical Experience with Autism

The emergent rationale for employing DHA/EPA for autistic spectrum disorder (ASD) and other pervasive developmental disorders (PDD) dates to 2001, with case histories provided independently by two research groups.[28] Vancassel et al reported low DHA (measured in plasma phospholipids), 20-percent lower-than-normal total omega-3s, and normal levels of omega-6 FAs in ASD children.[29] Bradstreet and Kartzinel reported finding omega-3 fatty acid deficiencies in nearly 100 percent of ASD cases.[30] Then in 2002, Hardy and Hardy claimed that, of 50 children diagnosed with PDD, 90 percent were deficient in RBC membrane DHA/EPA.[31] Various integrative physicians working with ASD and PDD patients have integrated DHA and EPA into their comprehensive regimens.[28]

A group in Austria conducted a six-week, double-blind RCT with 13 children, ages 5-17 years, diagnosed with ASD and displaying severe tantrums,



aggression, and self-injurious behavior.[32] Intervention was 1.5 g/day DHA/EPA (700 mg DHA and 840 mg EPA) or placebo. The DHA/EPA was well tolerated and there was a trend toward significant improvement over placebo for hyperactivity. The clinicians reported the small number of subjects may have statistically undermined the apparent clinical effects of the DHA/EPA.

Support for Adult Cognitive Performance

The brain's reliance on DHA/EPA continues throughout adult life. New research on primates and rodents has documented the adult brain cortex undergoes highly active synaptic turnover throughout life.[33] This finding has helped drive a paradigm shift in understanding brain plasticity. The new paradigm is one of high brain plasticity and adaptability.[33,34] It recognizes remarkable clinical observations on brain recovery following damage,[33] and relates this to rates of synaptic turnover as high as 350 percent per year observed in mammalian brains.[33,34] The central role that DHA plays in perinatal brain development may continue in the highly dynamic, healthy adult brain.

DHA and EPA Improve Cognitive Performance in Healthy Subjects

DHA and EPA are orthomolecules (*molecules orthodox* to the body) as defined by Pauling.[35] There is evidence that healthy individuals can expect cognitive benefit from orthomolecular medicine, including DHA/EPA.

Fontani et al conducted a double-blind RCT on 33 healthy volunteers ages 22-51 (average age 33).[36] For 35 days, subjects consumed either 4 g fish oil/day (providing 800 mg DHA and 1,600 mg EPA) or 4 g olive oil as placebo; dietary modifications were instigated via advice from a dietician. Subjects completed a mood questionnaire and took attention tests, and physiological recordings (electroencephalogram/EEG, electromyogram/EMG) were made at baseline and on day 35. The DHA/EPA group improved significantly over placebo on several mood parameters: vigor, anger, anxiety, fatigue, depression, and confusion. Measures of attention and reaction time were also improved. Participants demonstrated marked improvement in sustained attention and a significant reduction in errors on the attention test.

Significant improvements were also found on physiological measures that correlated with the test findings. Reaction time was significantly improved, as measured by EMG. The EEGs, which are typically hard to interpret, demonstrated the high-frequency beta-2 band was significantly reduced and the low-frequency theta and alpha bands were increased. The researchers tentatively interpreted these changes as consistent with omega-3 support for "direct action…on the central nervous system" leading to improved cortical function.[36] They concluded that DHA/EPA supplementation can improve higher brain functions – sense of wellbeing (vigor), reactivity, attention, cognitive performance, and mood – in young, healthy adults.[36]

DHA/EPA Intake May Lower Dementia Risk

Spanning at least the past decade, epidemiological studies indicate relatively high DHA and EPA intake is linked to lower relative risk of dementia incidence or progression. In 1997, Kalmijn et al reported on the Rotterdam Study.[37] In this longitudinal cohort study, 5,386 participants ages 55 or older were screened for dementia. Dietary habits were evaluated using a semi-quantitative food frequency questionnaire and then re-evaluated after 2.1 years. Fish consumption was inversely related to dementia incidence (RR=0.4, 95% CI=0.2-0.9), and more specifically to the risk of developing Alzheimer's disease (AD) (RR=0.3, 95% CI=0.1-0.9).

That same year (1997) yielded a report of the Zutphen Elderly Study, a smaller study also conducted in The Netherlands by Kalmijn's group.[38] They evaluated 476 men, ages 69-89 at baseline, performing cognition testing and correlating the data with food intakes reported in dietary histories. At baseline, high fish consumption was inversely associated with cognitive impairment. After three years, as with the Rotterdam study, high fish consumption was inversely associated with cognitive decline (RR=0.5, 95% CI=0.2-1.2). Omega-3 intake did not correlate with either measure.

A later analysis (after six years) of the Rotterdam Study data concluded that low intake of omega-3 fatty acids was not associated with increased risk for

dementia.[39] By contrast, a later analysis (after five years) of the Zutphen Elderly Study data confirmed the earlier finding, with consumers of fish showing a statistically significant ($p<0.01$) decrease in cognitive decline.[40] There was a linear relationship between DHA/EPA levels and cognitive decline – the higher the intake of DHA/EPA, the lower the rate of cognitive decline. Men who consumed an average of 400 mg fish omega-3s per day experienced significantly less cognitive decline compared with men who consumed an average of only 20 mg/day.

Taken at face value, this finding could suggest the range of DHA/EPA intakes currently recommended to reduce cardiovascular risk may be sufficient to help slow mental decline. The American Heart Association currently recommends a minimum of 57 mg/day DHA/EPA for healthy people (a total of 400 mg/week from two fish meals); a minimum of 1,000 mg/day for cardiovascular protection in patients with documented coronary heart disease; and 2,000-4,000 mg/day for patients with high triglycerides.[41]

Even modest fish intake might offer some protection for the brain. In a Chicago community study, 815 residents ages 65-94 were evaluated via a self-reported food questionnaire and tracked for an average 3.9 years.[42] A total of 131 participants developed AD. Those who consumed a fish meal once weekly had a statistically significant 60-percent decreased risk of Alzheimer's disease, compared with those who rarely or never ate fish (RR=0.4, 95% CI=0.2-0.9). Total omega-3 intake and DHA intake, but not EPA intake alone, were significantly associated with this lessened Alzheimer risk. This suggests an intake of as little as 30 mg/day DHA/EPA from fish might confer more protection against cognitive decline than eating no fish at all.

A follow-up of this community study at six years found fish consumption (one or more meals per week) resulted in a 10- to 13-percent slower rate of cognitive decline. There was no persuasive evidence for a more specific association with either DHA or EPA.[43]

In another longitudinal cohort study, serum phosphatidylcholine-DHA (PC-DHA) levels of 1,188 elderly Americans (average age 75 years) were analyzed at baseline and 10 years later.[44] Those in the lower half of the distribution of DHA levels at the time the first sample was taken, but who did not have AD at that time, appeared to have a 67-percent greater risk of developing AD within the subsequent 10-year period ($p<0.05$).

Longitudinal cohort studies can be more objective when blood or tissue is analyzed for specific nutrients. As part of the U.S. Framingham Heart Study, a cohort of 899 men and women (median age 76 years), who were free of dementia at baseline, were followed for a mean 9.1 years for development of all-cause dementia and Alzheimer's disease; the findings were published in 2006.[45] Ninety-nine new cases of dementia (including 71 of AD) occurred. Baseline and follow-up blood samples were tested for fatty acids in the plasma phospholipid fraction. After controlling for other variables, subjects in the upper quartile of plasma PC-DHA levels had approximately half the relative risk of developing all-cause dementia (RR=0.53, 95% CI=0.29-0.97; p=<0.04) compared to subjects in the three lower quartiles. The upper quartile (n=488) had a mean DHA intake of 180 mg/day and a mean fish intake of 3.0 servings per week ($p<0.001$).

Slowing Cognitive Decline in a Middle-Aged Population

Accelerated cognitive decline in middle age can make an individual more vulnerable to dementia in later life. Experts agree that once accelerated cognitive decline is reliably identified, intervention is advisable.[46] Evidence is accumulating to suggest omega-3 FA deficiency contributes to accelerated cognitive decline.

An epidemiology team led by Kalmijn tested 1,613 subjects, ages 45-70, for various cognitive functions at baseline and after five years and correlated the results with habitual food consumption reported on a self-administered food questionnaire.[47] Subjects exhibiting the most impaired cognitive function (lowest 10 percent of the group score) also had the lowest intake of DHA/EPA or fatty fish. Overall cognitive performance and psychomotor speed were positively correlated with DHA/EPA status. High intakes of cholesterol and saturated fat were both linked to increased cognitive impairment in this middle-aged population.

From 1987-1989, the Atherosclerosis Risk in Communities Study analyzed plasma fatty acids in cholesteryl esters and phospholipids in 2,251 residents of Minneapolis, Minnesota.[48] Subjects, average age 57 at baseline, all had some degree of heart disease.[48] Then from 1990-1992 and 1996-1998 the participants were tested for word recall, psychomotor speed, and verbal

fluency. Higher plasma omega-3 FA levels were correlated with reduced risk for decline in verbal fluency, particularly in hypertensive subjects and subjects with dyslipidemias.

The outcome of this study prompted an editorial in the *American Journal of Clinical Nutrition*.[49] Connor and Connor pointed out that the brains of AD patients have a lower content of DHA in the gray matter (more active zone), compared with individuals without Alzheimer's disease at death. They suggest dietary DHA entering the brain could correct DHA insufficiencies in cerebral cortical cell membranes. They also hypothesized dietary EPA could help counter pro-inflammatory processes contributing to neurodegeneration. The authors called for more clinical trials of omega-3 FAs in older adults at risk of cognitive decline and eventual dementia.

Mild cognitive impairment (MCI) is currently the condition most predictive for subsequent progression to dementia. MCI features severely impaired memory without substantial loss of other cognitive functions. Approximately 10-15 percent of MCI subjects progress to dementia within a year of diagnosis.[46] Individuals cognitively impaired but not demented tend to have abnormally low blood levels of DHA and EPA.[50]

A research group in Japan included MCI subjects in their prospective clinical trial on fatty acid therapy for memory-impaired patients. As background, Kotani et al determined experimental animals (rodents) show age-dependent increases in the peroxidative breakdown products from polyunsaturated fatty acids, not just of omega-3 DHA but also of omega-6 AA.[51] In a double-blind trial both these fatty acids were administered to a patient pool that included 21 with MCI, 10 with organic brain lesions, and eight with Alzheimer's disease. For 90 days, patients received either 240 mg/day DHA and AA (ratio not specified) or a 240 mg/day olive oil placebo. DHA and AA significantly benefited the MCI group compared to placebo on both attention and memory, while the organic brain-lesion group improved on memory alone; the AD group did not show benefit.[51]

Treating Dementia with DHA/EPA

Despite the fact abnormally low blood phospholipid-DHA levels are found in patients with AD or other dementias,[50] until recently few prospective trials had been conducted on DHA/EPA for dementia, and outcomes were inconclusive.

In 2006, a team from Stockholm's Karolinska University Hospital published a double-blind RCT of DHA and EPA for 174 patients with mild-to-moderate Alzheimer's disease.[52] Patients received either 1.7 g DHA and 0.6 g EPA daily or a placebo for six months, after which all received the DHA/EPA supplements for six more months. After the first six months, decline in cognitive function did not differ between groups. However, in a subgroup with less severe cognitive dysfunction (Mini-Mental State Exam score >27 points), a significantly slower decline was observed in the DHA/EPA group. A similar slowing was observed in the placebo group after crossover to DHA/EPA for the second six months. These findings suggest patients with mild Alzheimer deterioration could benefit from taking a mixed dietary supplement formulation containing both DHA and EPA.

In 2007, the Karolinska group reported specifically on the neuropsychiatric outcomes of the above trial.[53] The researchers found no overall treatment effect on neuropsychiatric symptoms, activities of daily living, or caregiver burden. They did find significant improvement of agitation in apolipoprotein E4 (APOE4) carriers and improvement of depression in non-APOE4 carriers.

Multiple sclerosis (MS) patients can exhibit dementia as a co-morbid condition, especially as the disease progresses. The etiology of MS and the prospects for its integrative management were reviewed in 2001.[54] Six decades ago, Swank designed a fat-restricted diet with similarities to a modern omega-3 enriched diet. Swank developed this innovative diet after noticing that coastal Norwegian residents consuming more fish and less animal fat had lowered risk for MS.[55] Beginning in 1948, Swank's patients were instructed to restrict animal fat intake and supplement liberally with cod liver oil (5 g/day); margarine and other hydrogenated oils were not allowed. Swank also encouraged three fish meals per week, and most patients increased their intake of fruits and vegetables. Over the ensuing decades,

Swank's patient population experienced a much lower rate of progression to advanced MS.

In 1988, Swank reviewed 150 of his patients followed for over 35 years.[56] Death rate was 31 percent, compared to the 80-percent predicted for MS patients not maintained on a diet. Of patients who commenced the restricted diet prior to developing disability, 95 percent had not progressed after three or more decades of being on the diet.

Other MS researchers published epidemiological evidence that, between 1949 and 1967, 20 countries including the United States had increased MS mortality risk associated with animal fat intakes and lowered risk with diets relatively high in fish and vegetables.[57]

Huntington Disease: EPA Shows Promise

Huntington disease (HD) features abnormal multiplication of a specific DNA sequence on chromosome 4: cytosine-adenine-guanine (CAG). Healthy people have just one CAG sequence at this spot; people with HD can have several dozen CAG sequences. As a rule, the more CAGs the HD patient has, the more severe their disease. The pathogenesis from genome to symptomatology is still poorly understood. On a suspicion that certain omega-3 responsive pathways could be involved, a team of British researchers have been using purified EPA in its ethyl ester form ("ethyl-EPA") as potential therapy for HD.[58]

Puri et al conducted a small RCT with ethyl-EPA on seven in-patients with advanced (stage III) HD.[58] After six months, the four patients who received ethyl-EPA demonstrated improvement on the orofacial component of the Unified Huntington Disease Rating Scale, while the three placebo patients had deteriorated ($p<0.03$). MRI brain scans revealed the placebo was associated with progressive cerebral atrophy and ethyl-EPA was associated with beneficial changes.

Three years later, the group completed a multicenter, double-blind RCT.[59] A total of 135 Huntington patients received either 2 g/day ethyl-EPA or placebo. The primary endpoint was the score at 12 months on the Total Motor Score 4 (TMS-4) subscale. The ethyl-EPA group as a whole failed to show statistically significant improvement on TMS-4. A subgroup including patients with fewer CAG showed significantly better TMS-4 improvement.[60]

The secondary endpoints in this trial suggested a significantly worse outcome from ethyl-EPA in behavioral severity and frequency compared to placebo.[59] This finding raises the question of whether a mixture of EPA and DHA, rather than a purified EPA, might have been more effective for this intractable disease.

Established Benefits in Affective Disorders

Numerous studies have examined the effects of DHA/EPA for affective disorders and have found them to be beneficial for mood management. Mood disorders that apparently respond to DHA/EPA include major depressive disorder, manic depression (bipolar disorder), and possibly also schizophrenia, borderline personality disorder (BPD), and anorexia nervosa.

Omega-3 Fatty Acids for Depression

As of mid-2007 (July), the peer-reviewed literature yielded seven double-blind RCTs of omega-3 fatty acids for MDD (summarized in Sontrop and Campbell[61] and Nemets et al[62]). Of these, six reported clinically significant benefits, including a trial with depressed children ages 6-12 years.[62] These trials admittedly were heterogeneous in size, design, and rationale, but from them a few trends emerged:

- DHA taken without EPA may not be sufficient to improve major depression.

- EPA taken without DHA sometimes gives benefit.

- The highest dosage of EPA did not necessarily yield the most benefit. In one double-blind trial, Peet and Horrobin[63] used a "dose-ranging" design, giving only EPA (as ethyl-EPA) at 1g/day, 2g/day, or 4g/day for 12 weeks, in addition to unchanged medication. The group receiving 1g/day demonstrated the most improvement, with more than half (53%) achieving a 50-percent reduction on the Hamilton Depression Rating Scale.

Maternal postpartum depression (also called "perinatal depression") has been linked to omega-3 FA deficiency. As reviewed in Freeman,[64] a survey of mother's milk in 23 countries determined that lower DHA content or lower seafood consumption was associated with higher rates of postpartum depression. Freeman noted that pilot trials of supplementation with DHA and EPA have produced mixed results and called for larger and better-designed trials to resolve this condition that endangers both mother and child.

Promise for Bipolar Disorder

Bipolar disorder (BD) with its complex spectrum of symptoms is likely associated with neural cell membrane dysfunction, most likely signal transduction abnormalities. A comprehensive 2004 review of integrative management of BD examined the extensive data for membrane abnormalities in BD and suggested supplementing with DHA/EPA as part of an integrative medical regimen.[65] Several case reports suggest flaxseed oil may trigger manic episodes in BD, a predilection first reported by Rudin in 1981.[66]

To date, four published double-blind trials on DHA/EPA for BD have been published. The first was a 1999 trial that found significantly longer remission of bipolar symptomology from a high-dose DHA and EPA mixture (9.6 g/day) compared to placebo.[67] Three more double-blind trials were published in 2006 with differing results. In the largest trial (75 patients), Frangou et al found significant improvement using EPA only (ethyl-EPA), with 1 g/day working just as well as 2 g/day.[68] Keck et al found no significant differences between placebo and 6 g/day EPA (no DHA) in 61 patients.[69] Marangell et al conducted a small study on 10 patients using only DHA and reported only that DHA was "well tolerated."[70]

A 2005, open-label trial, using EPA at 1.5-2.0 g/day as "add-on" therapy for BD, found that eight of 10 patients improved at least 50 percent on the depression scale.[71] This finding is in line with Frangou's double-blind trial outcome cited above.[68] In another open-label trial, children ages 6-17 years demonstrated a modest improvement in mania with intakes of 1.3-4.3 g/day DHA/EPA for eight weeks.[72] Taken altogether, the existing trials of DHA and EPA for bipolar disorder suggest efficacy, especially for the depression phase, with EPA appearing to be the most efficacious of the two.

The levels of seafood intake per capita in various countries of the world roughly correlate with the respective prevalence rates of BD in community samples.[73] The greater the seafood consumption per capita in a country, the lower the prevalence of bipolar spectrum disorders. Countries that consume a lot of fish on average (e.g., Iceland, Korea, and Taiwan) have relatively low incidence, while countries that consume very little fish (e.g., Germany, Switzerland, and Hungary) have up to seven times the incidence of countries with high fish intake. Noaghiul and Hibbeln estimated a "vulnerability threshold" for BD at seafood consumption below 50 pounds of seafood/person/year.[73]

In 2006, participants in the Omega-3 Fatty Acids Subcommittee, assembled by the Committee on Research on Psychiatric Treatments of the American Psychiatric Association, published an extensive assessment of the available data on the clinical use of omega-3 fatty acids in the prevention and/or treatment of psychiatric disorders.[74] This report included meta-analyses of RCTs conducted with DHA and/or EPA for major (unipolar) depression and bipolar depression. These meta-analyses found statistically significant benefit (p=0.02) from EPA and EPA/DHA. The Subcommittee found less persuasive evidence for benefit in schizophrenia.

Trials in Schizophrenia

Currently, six double-blind RCTs with DHA/EPA have been conducted, involving 390 patients with schizophrenia or schizoaffective disorder. Four of these documented clinical benefit from 2/g EPA daily for three months.[74-78] One trial found high-EPA fish oil performed better than high-DHA fish oil or placebo.[74] Another dose-ranging trial of ethyl-EPA found 2 g/day worked better than 1 g or 4 g daily. Two trials by the same group examined ethyl-EPA's effect on tardive dyskinesia associated with pharmaceutical management of schizophrenia. In a 2002 trial, Emsley et al found benefit at 3 g/day,[76] but a later 2006 trial did not demonstrate benefit at the lower dose of 2 g/day.[78]

A "phospholipid membrane hypothesis of schizophrenia" emerged in the late 1970s, as reviewed in 2000 by Fenton and colleagues.[79] This hypothesis encompasses abnormalities of long-chain omega-6 fatty

acids such as AA, as well as the omega-3 FAs DHA and EPA. Fenton et al list multiple analyses of RBC membranes (recognized markers for essential fatty acid status) that consistently document depletion of AA, DHA, and EPA. Also noted were studies documenting depletion in plasma, thrombocytes, and post-mortem brain tissue of schizophrenia patients.[79]

Elevations of membrane phospholipase A2 activity (measured in platelets) have been reported in schizophrenia, consistent with elevated membrane turnover of fatty acids.[79] These findings are reminiscent of the systemic membrane abnormalities observed in bipolar disorder.[65]

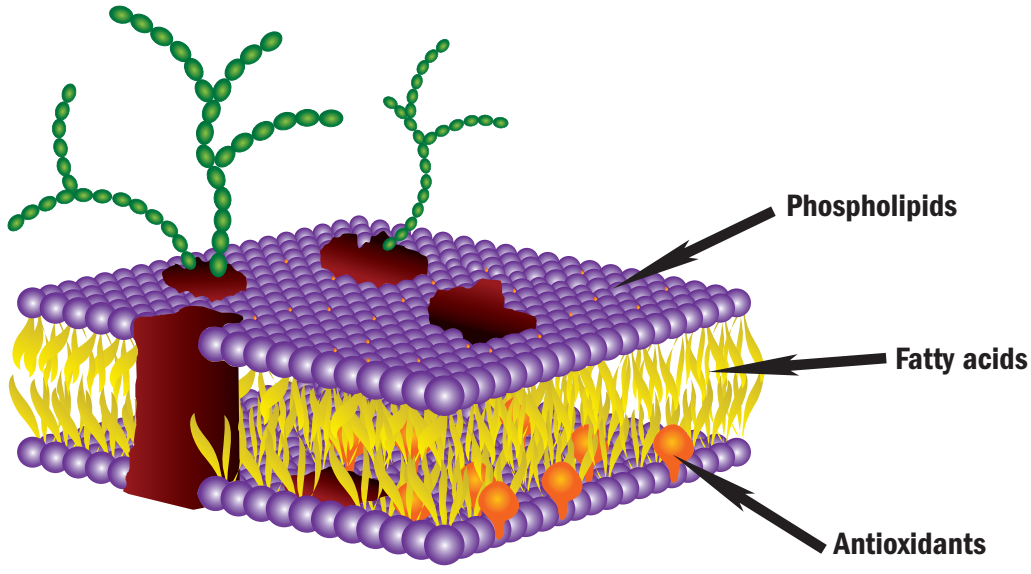
Perhaps the most compelling evidence so far of membrane abnormalities in schizophrenia are the findings from noninvasive nuclear magnetic resonance (NMR) procedures (summarized in Fenton et al[79]). These data suggest elevated membrane phospholipid breakdown products in the brain at an early stage of the illness and reduced levels of membrane phospholipid precursors. DHA and EPA are first-line nutrients for repairing damaged membranes and initial RCT outcomes suggest they deserve further study for the schizoaffective spectrum.

Cell membrane dysfunction is just part of an impressive body of evidence that strongly suggests schizophrenia is related to other affective disorders across a pathologic continuum. Striking genetic, symptomatic, and pathophysiological overlaps suggest the continuum to be unipolar (major) depression⇒bipolar disorder⇒schizoaffective psychosis⇒schizophrenia.[65] Although the degree of benefit or dosing strategy is not yet conclusive, findings that DHA and EPA have produced benefits for major depression, bipolar disorder, and schizophrenia justify their inclusion in a treatment protocol for affective disorders.

Borderline Personality Disorder

Borderline personality disorder may also respond to omega-3 supplementation. In a double-blind, placebo-controlled trial, 30 female subjects with moderately severe BPD received 1 g/day EPA only (as ethyl-EPA) or a placebo for two months. Those taking ethyl-EPA experienced significantly diminished aggression and less severe depression.[80]

Figure 2. Cell Membrane Schematic, Demonstrating the Intrinsic Structural Synergy of its Fatty Acids, Phospholipids, and Antioxidants ("Triple Cell Membrane Synergy")



DHA/EPA Support Cell Membranes, the Pacemakers of Metabolism

What are some of the mechanisms involved in the diverse therapeutic applications of omega-3 fatty acids? DHA and EPA literally feed cell membranes, the dynamic structures that manage the vast majority of life processes. Almost all the pivotal life processes occur in, on, or attached to membranes.[81] Membranes are literally the pacemakers of metabolism – a high metabolic rate correlates with high membrane unsaturation among vertebrate species.[82] Increasing unsaturation enables improved fluidity and more versatile cooperation between the "sea" of lipids in the membrane and the proteins immersed in this medium. Within the membrane-as-pacemaker, the polyunsaturated fatty acid content affects fluidity to enable the myriad membrane-bound enzymes, receptors, transporters, and other catalytic molecules.

Within the membrane bilayer, DHA and EPA are attached to the larger phospholipid molecules via ester bonds.[81] Phospholipids with their attached fatty acids are the molecular building blocks of the membrane (Figure 2). DHA and EPA interact with the other fatty acids in the membrane bilayer – saturates, monounsaturates (omega-9s), and polyunsaturates (omega-6s, minor omega-3s) – and membrane fluidity is a net outcome of all the electron densities. Carbon-carbon double bonds have high electron density and impart fluidity to the membrane. This property renders DHA (six double bonds) and EPA (five double bonds) the most highly fluidizing of the major membrane fatty acids.[82]

As a rule, the more fluid a membrane the more efficient its biochemical performance.[82] In general, experts agree the advanced human cell is only as efficient as its membrane system.[81,82] This life principle suggests that having adequate levels of DHA and EPA in membrane systems is crucial to the survival, growth, renewal, and myriad functions of human cells.

Relative Functional Significance of DHA, EPA, and ALA

The DHA and EPA content of cell membranes reflects ongoing dietary intakes. As dietary intakes change the membrane profile changes. Within the membrane, micro-distributions of the fatty acids attached to phospholipids are continually being fine tuned by enzymes (acyltransferases) that remove them from the tails of certain phospholipids and relocate them to others.[83]

Probably due to their highly fluidizing properties, DHA and EPA are found in highest concentrations in the most dynamic membranes (e.g., retina, brain, and spermatozoa). Beyond conferring membrane fluidity, DHA and EPA are orthomolecules that contribute to the homeostatic regulation of tissue performance, renewal, and regeneration. On the other hand, ALA is not found in high concentrations in cell membranes.

DHA and EPA can provide a degree of biochemical backup for each other. Although EPA may not be readily forward-converted to DHA, DHA is readily back-converted to EPA.[84] The limitations imposed by the poor conversion of ALA to either EPA or DHA, and by the sluggish conversion of EPA to DHA, suggest that intake of preformed DHA is needed to assure adequate supply to the brain, cardiovascular system, and other organ systems.

DHA/EPA Influence Inflammatory Balance

Eicosanoids are by definition metabolites of fatty acids. Healthy, non-inflammatory eicosanoid balance is maintained throughout the body by way of a homeostatic balance between omega-3 and omega-6 fatty acids in cell membranes. Eicosanoid balance then exerts a "downstream" balancing influence on cytokines (small protein messenger molecules). Of the omega-3 FAs, the shorter chain ALA is rarely found in cell membranes and has no identifiable metabolites that might contribute to homeostatic balance. Both DHA and EPA, on the other hand, are precursors of metabolite messenger molecules that have wide ranging physiological effects.

In the context of the modern human lifestyle and diet, the eicosanoid metabolites of EPA are crucial to provide anti-inflammatory effects by balancing the potentially pro-inflammatory eicosanoid metabolites of the omega-6 AA. It is important to stress that AA metabolites are not inherently dangerous to health, nor are they "bad" fatty acids. Rather, the organism requires AA for systemic homeostasis, and at higher dietary levels than omega-3 FAs. Unfortunately, modern dietary

patterns de-emphasize omega-3 intakes while over-emphasizing intakes of omega-6s and other fatty acids less important to homeostasis and total health.

The relatively "bad" factor in this scenario is the chronically unbalanced state of the standard American diet (SAD). The SAD confronts the consumer with: (1) an overall lack of natural fatty acids due to the consumption of "low-fat" foods; (2) an overload of trans-fatty acids, produced through hydrogenation and unnatural to cell membranes; or (3) a large imbalance of omega-6 to omega-3 FA intake, due to consumption of meats raised in feedlots rather than grass fed on the open range (meat from grass-fed cows has higher levels of omega-3 FAs). As a consequence, individuals who subsist on the SAD are at heightened risk for pro-inflammatory events that foster degenerative disease.

Simopoulos concluded from anthropological, epidemiological, and molecular-level studies that humans evolved on a diet with a ratio of omega-6:omega-3 FAs close to 1:1; whereas, in today's Western diets the ratio ranges from 15:1-17:1.[85] Simopoulos is part of a growing chorus against the SAD, asserting a preponderance of dietary omega-6 FAs predisposes tissues to inflammation and subsequent pathology.

In addition to such "acquired" dietary imbalances that lessen omega-3 intakes, the healthy human organism has limited capacity to elaborate the long-chain DHA and EPA from shorter-chain precursors. Metabolic biochemists have calculated that five percent or less of dietary ALA is converted to EPA, and less than 0.5 percent of dietary ALA makes it to DHA.[86] One approach to bypassing this problem could be to markedly increase the dietary intake of ALA. However, a study with lactating women found that high dietary ALA (10.7 g/day for four weeks) did not raise DHA levels in breast milk or RBCs.[9]

Docosanoids: Protective DHA Metabolites

DHA in the membrane is a source of metabolites with a novel stereospecificity unlike that of the known eicosanoids. Aptly christened docosanoids, they are chemical messengers with potent anti-inflammatory and other protective actions.[87] The three known classes of docosanoids – docosatrienes, resolvins, and protectins – are produced mainly from controlled oxidative breakdown of DHA within (or possibly adjacent to) the membrane. Of the protectins, neuroprotectin D1 (NPD1) is generated during stroke and counteracts pro-inflammatory gene expression that normally results from ischemic damage. This messenger substance also counteracts potential oxidative damage to DNA in the retinal pigment epithelium cells.[87,88]

Current research is focused on another class of docosanoid messengers, the resolvins. As their name implies, these molecules help resolve (terminate) ongoing inflammatory cascades.[88] Inflammation that terminates on a timely basis is homeostatic – and desirable. However, metabolic insults and imbalances can often prolong inflammation and trigger pathology. The physiological resolution of a well-orchestrated inflammatory response is essential to maintain homeostasis, and resolvins appear to be involved in this process.

The broader scientific literature on DHA confirms it is essential for normal neurological development, maintenance of learning and memory, and brain plasticity. DHA in neuronal membranes enhances synaptic membrane fluidity and function, regulates gene expression, mediates cell signaling, and enhances the electrical basis for memory formation.[89] In laboratory rats subjected to traumatic brain injury, prior dietary supplementation of DHA enhances recovery and boosts brain production of brain derived neurotrophic factor (BDNF), a major brain growth factor.[89] This array of protective and homeostatic activities, working in harmony with EPA, helps explain the wide range of whole-body benefits achieved by both.

Orthomolecular Synergy of Cell Membrane Nutrients

DHA and EPA have an obvious and predictable synergy with other cell membrane nutrients, specifically phospholipids and antioxidants. Depending on the requirements of the tissue in question, the phospholipids phosphatidylserine (PS), phosphatidylethanolamine (PE), and PC can carry substantial amounts of DHA in their "tail" positions, especially tail position 2. These phospholipid "parent molecules" also anchor EPA within the membrane.[81]

Healthy cells have a complement of antioxidants within their membranes that help protect them from destruction by intrinsic oxidants (obligatorily generated during routine metabolism) or extrinsic oxidants

imposed by lifestyle or the environment.[90] Membrane antioxidants are structurally intermingled with fatty acids and function as a protective "first line of defense."[81] In the presence of antioxidants, fatty acids with the most unsaturated bonds, namely DHA and EPA, are protected against oxidative ("free radical") destruction. Thus, within the dynamic membrane milieu, DHA and EPA exist in homeostatic synergy with both their parent phospholipids and the antioxidants dispersed in the membrane lipid bilayer, providing "triple cell membrane synergy." Thus, in addition to protective antioxidants, supplements that deliver DHA and EPA bound to phospholipids – such as omega-3s bound to phosphatidylserine and krill oil that contains omega-3 FAs bound to phospholipids – provide the building blocks for healthy cell membranes.

Omega-3 Phosphatidylserine (Omega-3 PS)

Phosphatidylserine is an important brain nutrient. At least 25 RCTs (reviewed in a recent book[46]), conducted over more than two decades, have established PS is beneficial for declining memory, learning, other cognitive functions, and mood and stress management. PS supports brain energetics and, at the tissue level, supports the receptors for many chemical transmitter systems. Neuron cell membranes, which are especially rich in PS, contain DHA in a proportion of the PS molecules (Figure 3).

Omega-3 PS Benefits AD/HD

Vaisman et al reported on a double-blind trial with omega-3 PS for AD/HD.[91] They recruited 60 children (3:1 ratio of boys:girls) with AD/HD-like symptoms (average age nine years). The children were randomized to three groups: (1) canola oil (controls), (2) fish oil (providing 250 mg DHA/EPA daily), and (3) an omega-3/PS combination (providing 300 mg PS and 250 mg DHA/EPA daily). No stimulant medications or other dietary supplements were administered during the trial period (80-100 days; average 91 days). The group receiving omega-3 PS had the highest proportion of children whose symptoms improved.

The children's sustained visual attention and discrimination were assessed using the Test of Variables of Attention (TOVA). The TOVA AD/HD Index "z" score improved over controls for both the omega-3 PS and the fish oil groups, but significantly more in the PS group ($p<0.001$). This indicates that omega-PS improved attention performance (and more dramatically than fish oil) compared to the control group. The omega-3 PS group also manifested a significantly higher ratio of symptom clearance than the control group, with 11/18 of the omega-3 PS children becoming asymptomatic versus 3/21 of the control children ($p<0.05$). Of the fish oil group, 7/21 became asymptomatic – not statistically significantly different from controls. Omega-3 PS ameliorated the inattention symptoms of AD/HD to a greater degree than equivalent amounts of DHA/EPA from other dietary sources.

Figure 3. Schematic of Omega-3 Phosphatidylserine (Omega-3 PS)

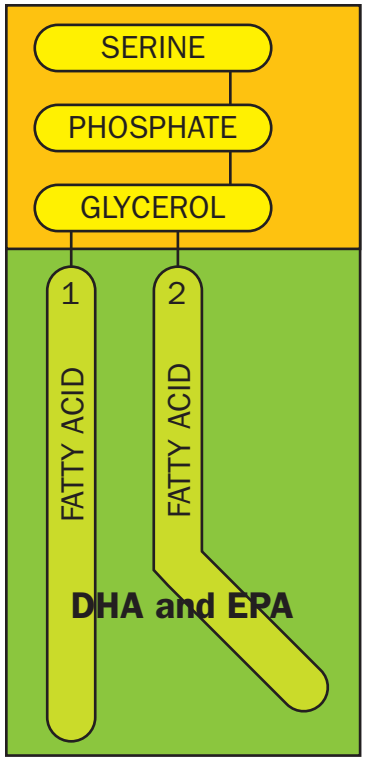
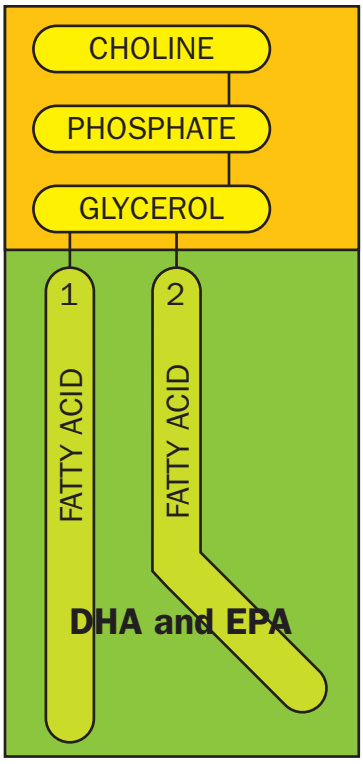


Figure 4. Schematic of Omega-3 PC Present in Krill Preparations



Omega-3 Phospholipids from Krill

Krill, small shrimp-like crustaceans, are ubiquitous in the oceans and are some of the planet's hardiest creatures. Krill sustains many marine animals and is a traditional food for humans. The Antarctic krill (*Euphausia superba*) live in the most frigid seas. Their cell membranes carry a high complement of DHA and EPA that render them highly fluid in order to function in ambient temperatures well below the freezing point.

Unlike typical fish oil supplements that carry almost no phospholipids, much of the DHA/EPA in krill oil is linked to phospholipids, particularly phosphatidylcholine (Figure 4) and in lesser amounts to phosphatidylethanolamine. The remaining DHA and EPA are in triglyceride form. The krill-phospholipid molecular fraction also includes the potent membrane antioxidant astaxanthin.

Krill omega-3 preparations have been tested in three double-blind trials – for premenstrual syndrome (PMS) mood management/dysmenorrhea, blood lipid management, and modulation of inflammatory symptoms and blood markers linked to arthritis. In two trials the krill complex was directly compared to fish oil.

Krill for PMS and Dysmenorrhea

PMS and dysmenorrhea are thought to affect 90 percent of reproductive-age women. Abnormal fatty acid metabolism has been implicated (reviewed in Sampalis et al[92]). A double-blind RCT was conducted with a krill omega-3 supplement (NKO®) on 70 healthy volunteers suffering from PMS/dysmenorrhea.[92] One group received a krill oil supplement while the other group received an equivalent amount of DHA and EPA as fish oil.

In the krill group, 36 women consumed 2 g/day krill oil with meals (providing 800 mg phospholipids and 600 mg omega-3 FAs). The fish oil group consumed 2 g/day fish oil (18:12; 18% EPA/12% DHA) with meals, providing 600 mg DHA/EPA. Subjects in both groups took supplements every day for the first 30 days, then for just 10 days per month during the succeeding two months (beginning eight days prior to expected menstruation). The women tracked mental and physical symptoms on a questionnaire developed by the American College of Obstetrics and Gynecology.[92]

Although the fish oil and krill groups both improved in weight, abdominal discomfort, and swelling, only the krill group experienced statistically significant improvements in breast tenderness, feelings of inadequacy, stress, irritability, depression, joint discomfort, and bloating. The krill group also reported more improved alertness, energy, and wellbeing. By conclusion of the study, the krill group consumed significantly fewer analgesic medications during the 10 perimenstrual days than the fish oil group. Unlike the krill group, 64 percent in the fish oil group complained of unpleasant reflux.[92]

Krill Supports Circulatory Health

Circulatory health is fundamental to brain health. Blood lipid abnormalities (elevated LDL and total cholesterol, reduced HDL, and high triglycerides)

contribute not only to morbidity and mortality associated with cardiovascular disease, but also to cognitive decline. In a double-blind trial, krill oil was compared to fish oil (18% EPA/12% DHA) in men and women with hyperlipidemia (total cholesterol above 194 mg/dL; triglycerides above 204 mg/dL).[93]

In this 90-day trial, two groups of subjects received krill at either 1-1.5 g/day or 2-3 g/day (depending on body mass index (BMI)), another group received 3 g/day fish oil, and a fourth group received placebo. At its lowest dosage (1-1.5 g/day), krill oil significantly lowered total and LDL cholesterol and elevated HDL cholesterol, compared to baseline and to the fish oil and placebo groups. At 2 g/day, krill also significantly lowered serum triglycerides in addition to cholesterol, while the highest krill intake (3 g/day) did not produce additional benefit over 2 g/day. The fish oil lowered cholesterol only marginally and failed to lower triglycerides below baseline values.

Anti-Inflammatory Effects

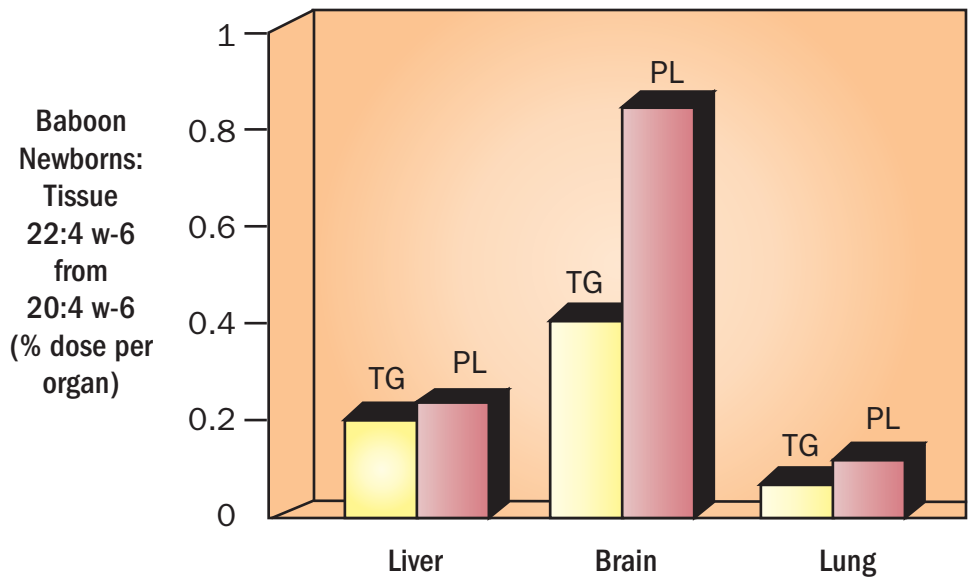
C-reactive protein (CRP) is a systemic inflammatory marker and a strong predictor of stroke and cognitive impairment.[94] In a double-blind RCT, krill oil demonstrated anti-inflammatory effects.[95] The study recruited a total of 90 subjects with cardiovascular disease, rheumatoid arthritis, or osteoarthritis, and high levels of CRP (>1.0 mg/dL). Subjects received a low dose of 300 mg/day krill oil or placebo and were assessed at baseline, 7, 14, and 30 days. By day 7, krill had significantly reduced CRP (by 19%; $p<0.05$) compared to placebo. The CRP reduction was more marked at day 30 (30% reduction; $p<0.01$) compared to placebo. Fish oil has failed to lower CRP in at least four studies.[96]

Omega-3 Phospholipids Target the Brain

Much evidence gleaned from animal studies (rodents and primates) indicates fatty acids are more bioavailable when provided in the form of phospholipids than as triglycerides or ethyl esters. In one study, brain fatty acid bioavailability was more than doubled by using phospholipids compared to triglycerides as the delivery form. This experiment compared tissue deposition of a fatty acid (arachidonic acid) in triglyceride form (as often found in fish oil) or phospholipid form, fed to neonatal baboons.[97]

Arachidonic acid is the predominant polyunsaturated fatty acid in the brain. As a major component of membrane phospholipids, AA is critical for membrane function and serves as a precursor for eicosanoids that play important roles in cell and tissue regulation. AA is also a precursor for longer-chain adrenic acid

Figure 5. Tissue Distribution of Radiolabeled Arachidonic Acid Fed to Neonatal Baboons as either Triglycerides (TG-AA) or Phospholipids (PL-AA)[97]



(C22:5; omega-6), which is also abundant in the brain. In the baboon experiment, AA was radioactively labeled, then incorporated into triglycerides (TG-AA) or phospholipids (PL-AA) and fed to the animals as a single dose of either TG-AA or PL-AA.[96] After 10 days the distribution of radioactivity was analyzed. As shown in Figure 5, the brain accumulated more than twice as much radioactivity from PL-AA as from TG-AA. This experiment demonstrated phospholipids improve fatty acid uptake into the primate brain.

Conclusion

DHA and EPA are clinically renowned for their cardiovascular protective properties. A recent systematic review evaluated the effects of fish oil consumption for primary and secondary prevention of adverse cardiovascular events.[98] It concluded that increased consumption of omega-3 fatty acids from fish or fish-oil supplements, but not from ALA, reduces rates of all-cause mortality, cardiac and sudden death, and possibly stroke; all with only minor adverse effects. The results of this current review suggest the brain benefits of DHA and EPA may eventually prove to be just as impressive as their benefits for the cardiovascular system.

What is the Correct Intake of DHA/EPA for Brain Benefits?

Technically, humans can synthesize EPA and DHA from the shorter-chain ALA, but the conversion efficiency is low, even in healthy individuals. Thus flaxseed oil as a source of ALA cannot be assumed to substitute for dietary sources of DHA/EPA. Foods high in omega-3 FAs or supplements with preformed DHA and EPA are required.

In regard to food sources of DHA/EPA, the standard American diet is unlikely to contribute more than 50-100 mg/day. Various "functional foods" have appeared with DHA/EPA added. Omega-3 eggs, for example, can be a significant source by providing greater than 200 mg of "omega-3" per egg. However, it may be necessary to confirm which omega-3 FAs are in the food (e.g., DHA/EPA or ALA). Further caution is advised to ensure that other ingredients in the food are healthful. For example, one heavily promoted omega-3 spread carries trans-fatty acids – a potential toxic counterbalance to the omega-3 benefits.

The current knowledge base on DHA/EPA for brain function does not generate a rational daily intake recommendation. Hibbeln, from his studies on national seafood intakes and affective disorder incidence, suggested pregnant women may want to consume a minimum 650 mg/day of DHA and EPA (with a minimum 300 mg/day of DHA) to prevent postpartum depression.[99] The existing recommendations for cardiovascular protection could be taken as a minimum for brain protection. In North America, the American Heart Association recommends a minimum intake of two fish meals weekly for primary cardiovascular protection and 1,000 mg/day of DHA/EPA for protection against a second heart attack.

The practicality of making dietary recommendations to eat fish as a primary source of DHA/EPA is threatened by the fact that suitable fish are increasingly expensive and hard to find.[100] The stocks of wild salmon and other species that are not contaminated with mercury or other pollutants are increasingly restricted. An alternative is to take dietary supplements rich in DHA/EPA, including the omega-3 phospholipid complex from krill.

While the wild salmon stocks are shrinking, concerns are being voiced about the increasing use of krill for aquaculture: salmon farming.[101] Krill is thought to be the largest single biomass on the planet and is a life-sustaining food for diverse marine animals. The Antarctic stocks (*Euphausia superba*) are estimated at 50- to 500-million metric tons.[100] The international organization Convention on the Conservation of Antarctic Marine Living Resources (CCAMLR), part of the Antarctic treaty network, was founded in 1982 primarily to protect krill. It has 24 member countries, including the European Union, Norway (a big krill fishing country), Russia, and the United States, as well as nine other nonvoting member countries. CCAMLR has set a sustainable harvest for krill in the Antarctic of 4.45 million tons. Although this level has still not been reached, the advent of massive krill fishing boats has greatly increased the capability to harvest Antarctic krill, and the CCAMLR is in the process of tightening its regulatory framework for krill conservation.

Cultivated microalgae are a good source of DHA. Although high doses of ALA can increase tissue EPA levels, ALA does not have the same effect on DHA

levels,[9] rendering supplementation necessary. How does one know whether supplementation is necessary? Physical signs and symptoms of deficiency include excessive thirst, frequent urination, rough dry hair and skin, and follicular keratosis.[14,18] RBC membrane content remains the most accepted laboratory measure. Harris developed an "omega-3 index" (RBC DHA/EPA) as a marker and perhaps also a risk factor for coronary heart disease.[102] He suggests adequate sufficiency is likely attained when DHA and EPA exceed eight percent of the total membrane fatty acids.

Although the current clinical literature on DHA and EPA for brain function is still relatively small compared to the literature on circulatory benefits, the weight of the current evidence strongly supports the utility of these conditionally essential nutrient orthomolecules for cognition, behavior, and mood, as well as for early brain development and overall mental performance.

The evidence presented in this review clearly suggests that the fundamental basis for applying DHA/EPA to human health is their presence in cell membranes. The cell membrane rationale for DHA/EPA also points to linked supplementation with their synergistic "parent" phospholipids, such as PS and PC. A further cell membrane synergy can be achieved by adding fat-soluble antioxidants, such as astaxanthin and other carotenoids, vitamin E, and coenzyme Q10. Implementing this triple cell membrane synergy promises to bring integrative medicine closer to healing the dysfunctional brain.

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